Noninvasive markers for staging fibrosis in chronic hepatitis B patients

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Summary

Background: *Noninvasive evaluation of liver fibrosis in chronic hepatitis B (CHB) is a growing research field. We planed to study and assess the act of some non-invasive forms in Egyptian patients with chronic hepatitis B.* **Patients and Methods:** *The present study involved 109 patients who had chronic hepatitis B infection. The scoring models involved; AST to ALT ratio (AAR), age-platelet index (API), AST-to-platelet-ratio-index (APRI) and Fibrosis-4 (FIB-4), transient elastography (TE) as non invasive indicators for staging fibrosis in chronic hepatitis B patients were measured in all patients. Agreement between the results of serum biomarker and those of transient elastography was assessed by Kappa (κ) index. The optimal cutoff points used for these tests were settled on by maximizing Kappa index. The performance of serum markers was judged by receiver operator characteristic (ROC) curves. The work of each manner for differentiating significant fibrosis, advanced fibrosis, and cirrhosis was weighted against.* **Results:** *API, APRI and FIB4 showed statistically significant differences (p-value <0.0001) in distinguishing significant fibrosis, advanced fibrosis, and cirrhosis, while AAR showed statistically insignificant differences (p-value >0.05) in that differentiation. The cutoff values of AAR, API, APRI and FIB4 showed a successive increase in values when the stage of fibrosis progressed from significant fibrosis to advanced fibrosis to cirrhosis. The AUROC in distinguishing significant fibrosis and advanced fibrosis was highest in APRI and higher in FIB4 than API while in distinguishing cirrhosis it was highest in API and higher in APRI than FIB4.* **Conclusion:** *API, APRI and FIB-4 could reliably distinguish significant fibrosis, advanced fibrosis and cirrhosis while AAR is not a reliable predictor to distinguish significant fibrosis or advanced fibrosis.*

Keywords: *Noninvasive markers; Chronic hepatitis B; Transient elastography; Liver fibrosis*

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Introduction

Hepatitis B virus (HBV) Infection remains an important health problem with significant morbidity and mortality[1]. Around two hundred and forty million people are chronic HBV surface antigen (HBsAg) carriers with a large regional variation[2]. The prevalence is decreasing in several highly endemic countries due to improvements in the socioeconomic status, the vaccination programs and possible effective antiviral treatments[3]. Although the biopsy taken from the liver is the "gold standard" for evaluation of hepatic fibrosis, yet this maneuver is with several drawbacks, as invasiveness, and danger of complications[4]. APASL, EASL and AASLD guidelines for HBV managing advise concerning of serum alanine transaminase (ALT), HBV deoxyribonucleic acid (DNA), hepatitis B e antigen (HBeAg) condition and/or necroinflammation/fibrosis grade of the liver when make a decision to antiviral therapy[5,6]. Liver biopsy has lately been confronted by the advance of new noninvasive methodologies which include hepatic stiffness measurements and several biomarkers of liver fibrosis, and

imaging techniques specially FibroScan[7,8]. FibroScan has been concluded to exactly mirror liver fibrosis; nevertheless, the use of it in obese is restricted, in addition to its relatively high cost[9]. However, the diagnostic accuracy of all non-invasive methods are better at excluding than confirming advanced fibrosis or cirrhosis[10,11]. The goal of the current study is an evaluation of the performance of APRI, FIB-4 and GPR in Egyptian patients with CHB cohorts.

Patients and Methods
Study design
This cross-sectional study was carried out at the Egyptian Liver Research Institute and Hospital (ELRIAH), Sherbin, El-Dakahlia, Egypt, Tropical Department and Internal Medicine Department, Mansoura University, Egypt. The study included one hundred and nine patients with chronic hepatitis B between March 2016 and November 2017. The inclusion criteria comprised: age more than eighteen years and chronic infectivity with hepatitis B, characterized by the existence of HBV-DNA in blood for more than six months. *The exclusion criteria* comprised existence of chronic HCV infection, hepatitis D virus, HIV co-infection, autoimmune liver disease, history of antiviral therapy, ascites, pacemaker, pregnancy, alcohol consumption ≥20g/day and NAFLD (identified by the existence of greater than five percent steatosis of hepatocytes). Liver function tests were done by commercially obtainable automated analyzers and hepatitis serological markers was tested using commercially obtainable enzyme-linked immunoassays. A minimum of three positive HBV DNA recordings was required for diagnosis of chronic HBV. Serum HBV DNA value was calculated in IU/mL and was assessed by a COBAS TaqMan model (Roche Diagnostics, Indianapolis, IN, USA), with lower detection border of 15 IU/mL.

Ethical Considerations
This work was carried out in harmony with the Helsinki Declaration, and was agreed by Mansoura ELRIAH Ethics and Mansoura university agency. An informed consent was obtained from all patients enrolled in this work.

Transient elastography (TE)
An intercostal space was used for accessing the right liver lobe of lying down patient. The patient was in the dorsal decubitus situation and the right arm in the utmost abduction position. By the guide of the FibroScan (Echosens, Paris, France), a part of liver of as a minimum 60 mm in thickness, lacking large vessels, was recognized for assessment. The rate of excellent assessment was estimated as the ratio between the numbers of validated to entire estimates. The outcomes were conveyed as a median value of the entire estimates in kilo Pascal (kPa). TE was considered reliable in the following situations: (i) 10 felicitous estimates; (ii) an interquartile range (IQR) lesser than thirty percent of the median value; and (iii) a success rate of >60%[12]. Hepatic stiffness was judged as the median of all suitable estimates. Cut-off points for classification of hepatic fibrosis in hepatitis B virus cases used in the current study was those of Xiao *et al.*[13] in their meta-analysis study. They are: *7.53 for detection of significant fibrosis (F2-3-4 METAVIR).*9.15 for detection of advanced fibrosis (F3-4 METAVIR). *12.17 for detection of cirrhosis (F4 METAVIR).

Serum noninvasive fibrosis markers
In the current study, the broadly used scores that could be estimated with usual laboratory tests were assessed. These scoring models involved AST to ALT ratio (AAR), age-platelet index (API), AST-to-platelet-ratio-index (APRI) and Fibrosis-4 (FIB-4) score.

The AST to ALT ratio (AAR)
It was believed that AAR might be the most basic noninvasive indicator used for expecting hepatic fibrosis. The AAR was applied for usage in chronic hepatitis C (CHC). An AAR equals or more than 1 is a mark for cirrhosis[14]. It was also useful in chronic hepatitis B and nonalcoholic steatohepatitis[15,16]. The equation used for determining the AAR is: AAR = AST (U/L) ÷ ALT (U/L)

The Age-Platelet Index (API)
The API was originally developed for usage in CHC to foretell cirrhosis[17]. Identification of cirrhosis by using a cutoff point ≥ 6 resulted in an area under the receiver operating curve (AUROC) of 0.91[18]. In chronic HBV, AUROC was 0.89 for recognizing cirrhosis in one research[19]. The equation used for determining the API is: **API** = Age Score + Platelet Score. **Age (years)**: <30 = 0; 30 - 39 = 1; 40 - 49 = 2; 50 - 59 = 3; 60 - 69 = 4; ≥ 70 = 5. **Platelet count (K/μL)**: ≥ 225 = 0; 200 - 224 = 1; 175 - 199 = 2; 150 - 174 = 3; 125 - 149 = 4; < 125 = 5.

The AST-Platelet-Ratio-Index (APRI)

The APRI was originally developed for usage in CHC patients in which Ishak ≥ 3 with significant fibrosis and Ishak ≥ 5 with cirrhosis as cutoff points[20]. Originally, the AUROC for significant fibrosis and cirrhosis was 0.80 and 0.89 using a cutoff ≥ 1.5 and a cutoff ≥ 2.0 respectively. Also in chronic hepatitis B, APRI has been studied in a large meta-analysis[21] with an AUROC for significant fibrosis and cirrhosis was 0.79 and 0.75 using a cutoff 1.5 and 2.0 respectively. The equation used for determining the APRI is: $\textbf{APRI} = $ [AST (U/L) $\div$ULN of AST (U/L)] $\div$ [Platelets (K/µL)].

Fibrosis-4 Index (FIB-4)

Fibrosis-4 was at first builded up in cohorts of chronic HCV/HIV patients[22], and then applied in chronic HCV infected patients alone[23]. It gave up an AUROC of 0.85 and 0.91 for severe fibrosis (METAVIR F ≥ 3) and cirrhosis (METAVIR F4) respectively. The cutoff point FIB-4 equal to or more than 3.25 was applied for determining advanced fibrosis (Ishak equal to or more than 4) in the preliminary mono-infected HCV research. In chronic hepatitis B, the mean AUROC for cirrhosis is 0.84 (24). The equation used for determining the FIB-4 index is: $\textbf{FIB-4} = $ Age $\times$ AST (U/L)$\div$ Platelets (K/µL) $\times$ [$\sqrt{}$ALT (U/L)].

Statistical Analysis

Statistical analyses were done by version 21, SPSS (Statistical Package for Social Sciences) (IBM Corp., United States of America). Continuous variables were registered as median (IQR). Categorical variables were reported as frequency (%). The significance level was calculated when p≤ 0.05 supposing two tailed tests. The performance of serum markers was calculated with receiver operator characteristic (ROC) curves. A patient was regarded as positive or negative in proportion to whether the noninvasive manner value was more than, less than or equal to a given cutoff point. The ROC curve is a scheme of sensibility v's (1-Specificity) for all potential cutoff points. The wide spread accuracy index is the area under the ROC curve (AUROC), values near to 1.0 pointing to great diagnostic accurateness. For each serum biomarker level, sensibility and specificity were calculated for each threshold. Agreement between the results of serum biomarker and those of FibroScan was assessed by Kappa (κ) index. The optimal cutoff values used for each test were estimated by maximizing Kappa index. Positive (PPV) and negative predictive values (NPV) were computed from these cutoff values.

Results

Table (1) shows that, this study included 109 chronic hepatitis B patients with 85 males (78%); mean age 40 years; mean body mass index (BMI) 28.75 kg/m², mean ALT level 24 U/L, mean AST level 24 U/L, mean serum albumin level 4.38 gm/dl, mean platelets 208,000/ cmm^3. Table (2) shows that, API, APRI and FIB4 showed statistically significant diagnostic value (p-value <0.001 for all) in differentiating F01 from F234 with sensitivity (40.0%, 65.7% and 65.7% respectively) and specificity (94.6%, 97.3 and 87.8% respectively), while AAR showed statistically non significant diagnostic value (p-value= 0.721). Moreover, when differentiating F012 from F34, API, APRI and FIB4 showed statistically significant diagnostic value (p-value <0.001 for all), with sensitivity (48.1%, 66.7 % and 59.3% respectively) and specificity (93.9 %, 97.6% and 95.1% respectively), while AAR showed statistically non significant diagnostic value (p-value= 0.631). Also, when differentiating F0123 from F4, we found that, API, APRI and FIB4 showed statistically significant diagnostic value (p-value <0.001 for all), with sensitivity (57.1%, 71.4 % and 64.3 % respectively) and specificity (89.5 %, 89.5% and 93.7% respectively), while AAR showed statistically non significant diagnostic value (p-value= 0.061). The cutoff values of AAR, API, APRI and FIB4 showed successive increase in values when stage of fibrosis progressed from F≥ 2 to F≥ 3 to F4. The AUROC and 95% CI in differentiating F01 from F234, and in differentiating F012 from F34 was highest in APRI and higher in FIB4 than API while in differentiating F0123 from F4 it was highest in API and higher in APRI than FIB4.

Table (1) Baseline characteristics of study patients.

Characteristic	Value
All patients	109
Male Gender	85 (78.0%)
Age (years)	40.0 (16.5)
BMI (kg/m²)	28.75 (8.12)
ALT (U/L)	24.0 (17.0)
AST (U/L)	24.0 (14.0)
S. albumin (g/dL)	4.38 (0.51)
Platelets (/cmm3)	208.0 (87.0)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index.

Table (2) Diagnostic test evaluation

Fibrosis Stage	Marker	Cut off	Se (%)	Sp (%)	PPV (%)	NPV (%)	AUROC	95% C.I.	Sig.
	AAR	1.433	17.1	91.9	50.0	70.1	0.479	0.358-0.599	0.721
	API	4	40.0	94.6	77.8	76.9	0.760	0.660-0.860	<0.001
F≥2	APRI	0.464	65.7	97.3	92.0	85.7	0.843	0.755-0.931	<0.001
	FIB-4	1.346	65.7	87.8	71.9	84.4	0.792	0.692-0.892	<0.001
	AAR	1.503	22.2	92.7	50.0	78.4	0.531	0.402-0.660	0.631
	API	5	48.1	93.9	72.2	84.6	0.797	0.701-0.894	<0.001
F≥3	APRI	0.594	66.7	97.6	90.0	89.9	0.857	0.763-0.951	<0.001
	FIB-4	1.897	59.3	95.1	80.0	87.6	0.832	0.728-0.935	<0.001
	AAR	1.533	28.6	91.6	33.3	89.7	0.655	0.514-0.796	0.061
	API	6	57.1	89.5	44.4	93.4	0.863	0.777-0.948	<0.001
F4	APRI	0.697	71.4	90.5	52.6	95.6	0.856	0.746-0.966	<0.001
	FIB-4	2.286	64.3	93.7	60.0	94.7	0.836	0.709-0.963	<0.001

Abbreviation: AUSROC refer to area under summary receiver operating characteristic *curve*

Discussion

Histological diagnosis of hepatic fibrosis is necessary for chronic hepatitis B treatment as well as prognosis. At present, biopsy from the liver is still the gold standard for evaluating liver fibrosis. Nevertheless, this approach is an invasive, complicated manner[4]. So, as substitutes to liver biopsy, numerous noninvasive means and scoring models have been applied to assess liver fibrosis[7,8]. Regarding differentiating significant fibrosis (F≥2), the AUROC value in this study of APRI was higher than that of FIB-4 (0.79 vs. 0.84) which does not match with Xiao *et al.*[24], who showed that the mean AUSROC value for predicting significant fibrosis of FIB-4 was more than that of APRI

(0.76 vs. 0.72). While in a study done by Teshale *et al.*[25], the AUROCs in discriminating significant fibrosis were 0.81 for APRI and FIB-4, while the AUROCs in discriminating significant fibrosis was 0.56 for AAR which is better than AUROC of this study (0.479). Also, in a retrospective study by Ma *et al.*[26], the FIB-4 showed an area under the receiver operator characteristic (AUROC) of 0.79, to differentiate significant fibrosis from advanced fibrosis and cirrhosis which was similar to the result in this study. In a meta-analysis by Jin *et al*[21], the APRI yielded AUROCs for significant fibrosis of 0.79. Another meta-analysis by XY *et al.*[27] showed large variation in AUROC values of APRI, as they ranged from 0.61 to 0.86 for significant fibrosis which might be caused by considerable heterogeneity in the studies involved. A meta-analysis by Li *et al.*[28], studied the value of the FIB-4 index for staging fibrosis in hepatitis B virus patients gave an AUROC value of 0.78 for significant fibrosis. This study showed AUROC in API for significant fibrosis of 0.76 while a study by Erdogan *et al.*[29] found that API was not adequate for evaluation of significant fibrosis in CHB with an AUROC value of 0.53. Regarding differentiating advanced fibrosis (F≥3), the AUROC value of APRI was more than that of FIB-4 (0.857 vs. 0.832) which does not match with a meta-analysis done by Xiao *et al.*(24) which stated that the mean AUSROC value of FIB-4 was more than that of APRI (0.8 vs. 0.76) for foretelling significant fibrosis. The AUROC in this study was better. Regarding differentiating cirrhosis (F4), the AUROC value of APRI was more than that of FIB-4 (0.856 vs. 0.836) which does not match with a meta-analysis done by Xiao *et al.*[24] which stated that the mean AUSROC value of FIB-4 was more than that of APRI (0.78 vs. 0.72) for foretelling significant fibrosis. The AUROC in this study was better. In a study done by Kim *et al.*[19] AUROC for liver cirrhosis of AAR had a value of 0.68 which is nearly similar to the result of this study and had a value of 0.75 for APRI which is less than AUROC of this study (0.856), whilst the ROC curve of API showed a high value of AUROC at 0.889 which is a little more than AUROC of this study (0.86). In a meta-analysis by Jin *et al.*[21], the APRI gave AUROCs for cirrhosis of 0.75. Another meta-analysis by XY *et al.*[27]

showed broad difference in AUROC values of APRI, as they ranged from 0.50 to 0.83 for cirrhosis which might be caused by considerable heterogeneity in the studies involved.. A meta-analysis by Li *et al.*[28] yielded an AUROC value of 0.89 for cirrhosis. Overall, the current study showed that APRI had a better performance more than FIB-4 which does not correlate with a meta-analysis of Houot *et al.*[30] who concluded that APRI had lesser performances than FIB-4. Regarding AAR, this study showed poor results for significant and advanced fibrosis (AUROC of 0.48 and 0.53 respectively) which correlates with Eminler *et al.*[31] who concluded that AAR carried out inferiorly to other blood-based non-invasive tests in HBV patients. Also, the capability of AAR to make a diagnosis of significant fibrosis in HBV patients was poor in a study by Teshale *et al.*[25] with an AUROC of 0.56.

Conclusion
API, APRI and FIB-4 could be a reliably and easily available method to assess liver cirrhosis, while AAR is not a reliable mean for prediction of hepatic fibrosis.

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